



PATIENT INFORMED CONSENT FOR CLINICAL RESEARCH

Phase I/II Study of Everolimus and Intravesical Gemcitabine in BCG-Refractory Primary or Secondary Carcinoma In Situ of the Bladder (Phase I patients)

You have been asked to participate in a research study. In order to decide whether or not you should agree to be part of this research study, you should know enough about its risks and benefits in order to make a sound judgment. This process is known as informed consent.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your healthcare team. If you have any questions, you can ask your study doctor for more explanation.

This consent form gives you detailed information about the research study. Once you understand the study, its risks, and its benefits, you will be asked to sign the form if you wish to take part. You will be given a copy to keep.

You are being asked to take part in this study because you have carcinoma in situ of the bladder and have relapsed after receiving intravesical BCG.

Why is this study being done?

The purpose of this study is to test the safety of gemcitabine applied to the bladder directly combined with different oral doses of everolimus and to assess the right doses that you should be taking. Gemcitabine will be given at a fixed dose. Up to 3 dose levels of everolimus will be evaluated. This is a Phase I study. Phase I studies are done on small groups of patients to test the safety of the drug. In a previous study, Gemcitabine applied directly to the bladder was shown to have efficacy in patients with high risk superficial carcinoma in situ.

Gemcitabine is a standard chemotherapy drug that is commonly used to treat carcinoma in situ of the bladder. Everolimus is a pill that works by shutting down some of the pathways in cancer cells that make tumors grow.

Standard management for patients with high-risk superficial disease who fail BCG therapy is removal of the bladder (cystectomy). There are a few drugs for patients who fail intravesical BCG (drug placed directly into the bladder through a small catheter), none of which eliminates the need for cystectomy. Surgery results in impotence in men due to the need to remove the prostate as part of the surgical procedure.



Is there a potential conflict of interest for this study?

There are no known investigator and/or institutional conflicts of interest for this study.

How many people will take part in the study?

About 45 people will take part in this study at Memorial Sloan-Kettering Cancer Center. At the beginning of the study (Phase I), a minimum of 2 and a maximum of 18 patients will be treated with gemcitabine and a low dose of everolimus. If this treatment does not cause bad side effects, the dose of everolimus will slowly be made higher as we enroll the rest of the patients into the study.

What will happen if I take part in this research study?

Before you begin the study ...

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

Within 7 days of starting treatment:

- Pregnancy test (if you are able to become pregnant)

Within 14 days of starting treatment:

- Medical History
- Physical examination
- Blood samples
- Urinalysis
- MSKCC confirmation of diagnosis

Within 30 days of starting treatment:

- An electrocardiogram (or EKG) to check the electrical activity of your heart
- Chest X-Ray
- Cystoscopy (allows your doctor to see inside of your bladder by gently inserting a scope (a thin tube-like instrument with a light and tiny camera attached to it) into the bladder through the urethra)
- Transurethral Resection (TUR) of the bladder tumor
- Pulmonary function tests
- Hepatitis B and hepatitis C testing

During the study...

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.



- Gemcitabine will be placed directly into the bladder through a small catheter twice a week for 3 weeks, followed by a week of rest from gemcitabine. This will total 6 treatments in cycle 1. After 1 week of rest, the second cycle will begin. The total number of gemcitabine treatments will be 12 (2 cycles).
- Gemcitabine will be given in the outpatient (office) setting.
- You will be given a bottle of everolimus tablets to take home with you. Each bottle will contain enough tablets for one 28-day treatment period.
- Everolimus tablets should be taken either every other day or every day by mouth, followed by a big glass (16 fluid ounces) of water.
- Do not miss any tablets.
- You should take everolimus in the morning, at about the same time each day.
- Always follow the instructions for use of everolimus given to you by your study doctor.
- Pill diary: At the beginning of every treatment period, you will be given a form to document that you have taken your everolimus. This form must be completed and returned to your study doctor after every treatment period.
- You must bring back any pills you did not take.
- Biopsies from the bladder will be obtained and will be sent for further testing.

When I am finished taking Gemcitabine...

You will see your doctor every month to have your vital signs taken and get bloodwork drawn. You will get urine tests, cystoscopy (view of the bladder), urine cytology (test to detect presence of cancer in urine), and chest x-ray every 3 months. If a suspicious or positive cystoscopy or cytology is found, then a TUR will be performed no later than 4 weeks from the test to determine presence or absence of disease. You may be asked to continue to take Everolimus alone for up to 12 months.



Visit Schedule

Evaluation	Screening	Pre-Treatment Exams, Tests, or Procedures			Cycle 1 (Weeks)				Cycle 2 (Weeks)				Months											
		Within 30 Days	Within 14 Days	Within 7 Days	1	2	3	4 ¹	5	6	7	8 ¹	3	4	5	6	7	8	9	10	11	12		
Informed Consent	X																							
ECG	X																							
Pulmonary Function Test		X																						
Chest X-Ray		X											X			X			X				X	
Urine Culture		X																						
Urine Tests		X											X			X			X				X	
Cytoscopy		X											X			X			X				X	
Hepatitis B and Hepatitis C Testing		X			X			X					X											
Transurethral Resection (TUR)		X																						
Blood Tests			X				X				X		X	X	X	X	X	X	X	X	X	X	X	
Complete History			X																					
Physical Exam			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Toxicity Assessment						X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test				X																				
Gemcitabine			X		X	X	X		X	X	X													
Everolimus					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

¹ 1 week of rest from gemcitabine. There is no week of rest from Everolimus, which is taken continuously.





How long will I be in the study?

You will be asked to take Gemcitabine and everolimus for 2 months, and everolimus for a total of 12 months. After you are finished taking Gemcitabine and everolimus, you will receive vitals, bloodwork, urine cytology, toxicity assessment, cystoscopy and cytology every 3 months for another 12 months. If a suspicious or positive cystoscopy or cytology is found, then a TUR will be performed no later than 4 weeks from the suspicious/positive test to determine presence or absence of disease.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the Gemcitabine and everolimus can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what followup care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.



What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the Gemcitabine and everolimus. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the **Gemcitabine** include those which are:

Likely

- Lowering of the white cell, red cell, and platelet counts
- Nausea
- Vomiting
- Fatigue
- Loss of Appetite
- Rash
- Flu-like symptoms

Less Likely

- Leg swelling
- Constipation
- Mouth sores
- Numbness and tingling in your hands and feet
- Abnormal liver function tests
- Hair loss
- Allergic reaction
- Irritation of the veins
- Infection
- Protein/blood in the urine

Rare but serious

- A rare syndrome called hemolytic uremic syndrome which can lead to kidney failure has been reported

Severe shortness of breath due to fluid or scarring in your lung

Risks and side effects related to the **Everolimus** include those which are:



Likely

- Fatigue
- Nausea and vomiting
- Mouth ulcers
- Skin rash
- Headache
- Loss of Appetite
- Diarrhea
- Anemia

Less Likely

- Lowering of the white cell, red cell, and platelet counts
- Infection
- Increase cholesterol level
- There may be an increased level of certain liver enzymes
- There may be a decreased level of nutrients in the blood, such as calcium and magnesium.
- There may be elevations in your blood sugar levels.
- Cough
- Shortness of breath
- Inflammation in the lung which can cause shortness of breath or require oxygen. This condition is frequently mild and resolves once the study drug is stopped.

Rare but serious

- Fever and chills
- Blood clots
- Rash that is severe
- Mouth sores that are severe
- Nose bleeding
- Blood in urine
- Chest pain
- Kidney damage and/or failure of the kidneys

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

For more information about risks and side effects, ask your study doctor.



Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. We do know that the information from this study will help doctors learn more about Gemcitabine and Everolimus as a treatment for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

Every effort will be made to keep your study records private. It is the responsibility of the research staff at Memorial Hospital to make sure that your records are managed to protect your privacy. If information from this study is used in any reports or publications, your name and anything else that could identify you will not be used. Trained staff at Memorial Hospital may review your records if necessary. Access to your medical information will be limited to those listed in the Research Authorization Form, which is a part of the informed consent process.

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Novartis, Inc. will supply everolimus free of charge. You and/or your insurance company will be responsible for paying for the gemcitabine applied directly to the bladder, and administration of the gemcitabine applied directly to the bladder.

If, during the study, everolimus becomes approved for use in your cancer, you and/or your health plan may have to pay for drug needed to complete this study.

You will not be paid for taking part in this study.

What happens if I am injured because I took part in this study?



You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor Guido Dalbagni, MD at (646) 422-4394.

Any hospital that does research on people has an institutional review board (IRB). This board reviews all new studies to make sure that the patient's rights and welfare are protected. The IRB at MSKCC has reviewed this study.

For a non-physician whom you may call for more information about the consent process, research patients' rights, or research related injury is Jorge Capote, RN, Patient Representative, telephone number: (212) 639-8254.



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Statement of professional obtaining consent

I have fully explained this research study to the research participant or guardian of research participant _____. In my judgment and the research participant’s or guardian’s, there was sufficient access to information, including risks and benefits to make an informed decision.

Date: _____ Consenting Professional Signature: _____

Consenting Professional Name: _____
(Print)

Research Participant (or guardian’s) statement

I have read the description of the clinical research study or have had it translated into a language I understand. I have also talked it over with the consenting professional to my satisfaction. I understand that my/the research participant’s participation is voluntary. I know enough about the purpose, methods, risks, and benefits of the research study to judge that I want (the research participant) to take part in it.

Research Participant number: _____ Research Participant Signature: _____

Date: _____ Research Participant Name: _____
(Print)



RESEARCH AUTHORIZATION

Phase I/II Study of Everolimus and Intravesical Gemcitabine in BCG-Refractory Primary or Secondary Carcinoma In Situ of the Bladder (Phase I patients)

Research Participant Name: _____

Research Participant MRN : _____

We understand that information about you and your health is personal. We are committed to protecting the privacy of your information. Because of this commitment, we must obtain approval from you before we can use your protected health information for research purposes. This form provides that authorization. This form also helps us make sure that you are informed of how this information will be used or disclosed in the future. Please read the information below carefully before signing this form.

USE AND DISCLOSURE COVERED BY THIS AUTHORIZATION

A representative of Memorial Sloan-Kettering Cancer Center must answer these questions completely before providing this authorization form to you. PLEASE DO NOT SIGN A BLANK FORM. You or your personal representative should read the descriptions below before signing this form.

Who will have access to and/or use your health information?

The following individuals and/or organization(s) may have access to use, disclose or receive some information about you. They may only share the information to the individuals/parties indicated on this list. This information must be shared with you, the research subject and/or your personal representative, as required by law.

- Every research site for this study, including Memorial Sloan-Kettering Cancer Center and the research support staff (for example, research study assistant) and medical staff at each location
- Every health care personnel who provides services to you in connection with this study
- Any laboratories, other individuals/organizations that analyze your health information in connection with this study as defined by protocol
- The following research sponsors: Memorial Sloan-Kettering Cancer Center
- The National Cancer Institute and/or the National Institute of Health
- The United States Food and Drug Administration and other regulatory agencies responsible for oversight.
- The members and staff of the hospital's Institutional Review Board and Privacy Board



Memorial Sloan-Kettering Cancer Center
IRB Protocol

IRB#:10-165A(1)

- Principal Investigator and Co-Principal Investigator(s): Guido Dalbagni, MD, Matthew Milowsky, MD, Dean Bajorin, MD
- Members of the Research Team including the participating investigators, research assistants, clinical nurses, fellows/residents, and clerical support staff.
- Members and staff of the hospital's Office of Clinical Research, Computing Resource Group that manages research databases, and the research management and support staff in the clinical departments
- Members of the Hospital's Data Safety Monitoring Board/Committee and Quality Assurance Committee
- Others (as described below):
 - Novartis, Inc.

What information will be used or disclosed?

The boxes checked below should provide you with enough detail so that you can understand what information may be used or disclosed.

- Your entire research record
- Any part of your medical records held by the hospital
- HIV-related information. This includes any information indicating that you have had an HIV-related test, or have HIV infection, HIV-related illness or AIDS, or any information which could indicate that you have been potentially exposed to HIV. (New York State requires us to obtain special consent)
- Pill diaries, blood, and tissue.



SPECIFIC UNDERSTANDINGS

By signing this form, you give permission for the sharing of your protected health information noted above. The purpose for the use and disclosure of your information, is to conduct the research study explained to you during the informed consent process. This form also ensures that the information relating to the research is available to everyone who may need it. Your protected health information may also be used for your research treatment, to collect payment for your treatment while on the study (when applicable), and to run the business operations of the hospital.

Once we have shared your information with the individuals and organizations listed on this form, they may be able to share your information again, if they are not subject to laws that protect your privacy.

It is your right to refuse to sign this authorization form. If you do not sign this form, you will not be able to participate in the research study. You will not receive the research treatment that was described to you. Your health care outside the study will not be affected. The payment for your health care or your health care benefits will not be affected.

If you sign this authorization form, you will have the right to withdraw it at any time. To withdraw the authorization will prohibit further use or disclosure of your health information. If the hospital has already used your health information approved by your authorization or needs the information to fulfill an obligation or analyze the data, the use or disclosure cannot be stopped. This authorization form will not expire unless you withdraw it. If you want to withdraw this authorization, please write to Guido Dalbagni, MD, Department of Surgery at the hospital.

You have a right to see and copy your health information described in this authorization form in accordance with the hospital's policies. You also have a right to receive a copy of this form after you have signed it.

Notice Concerning HIV-Related Information

If you are authorizing the release of HIV-related information, you should be aware that the individuals/organizations are prohibited from sharing any HIV-related information without your approval unless permitted to do so under federal or state law. You also have a right to request a list of people who may receive or use your HIV-related information without authorization. If you experience discrimination because of the release or disclosure of HIV-related information, you may contact the New York State Division of Human Rights at (800) 523-2437 or (212) 480-2493 or the New York City Commission of Human Rights at (212) 306-7450 or (212) 306-7500. These agencies are responsible for protecting your rights.



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IRB Protocol

IRB#:10-165A(1)

SIGNATURE

I have read this form and all of my questions have been answered. By signing below, I acknowledge that I have read and accept all of the information above.

Signature of Research Participant or Personal Representative

Print Name of Research Participant or Personal Representative

Date

Description of Personal Representative's Authority